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COMPLETE SPECIFICATION

Imides of Substituted Dicarboxylic Acids and process of producing the same

I, RICHARD KWIZDA, an Austrian citizen of Dr. Karl Lueger-Ring 6, Vienna I, Austria, trading as F. JON KWIZDA, do hereby declare the invention, for which I pray that a patent may be granted to me and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a new class of imides, more particularly imides of certain dicarboxylic acids, which are substituted by imide groups which have been derived from specific cyclic dicarboxylic acids. The invention relates also to a process of producing these novel compounds.

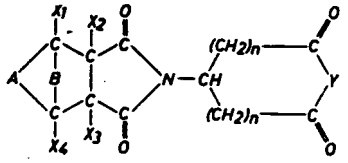
Some known substituted succinimides and glutarimides which contain phthalimide groups in the alpha or beta position have a tranquilizing activity on certain portions of the central nervous system and differ from other conventional sedatives and hypnotics, such as barbituric acids and hydantoins, in that the action is not accompanied by an initial excitation phase and there is a complete absence of narcotic or peripheral paralytic effects. Besides, these compounds have an extremely low acute toxicity and basically differ also in this respect from other previously used drugs having the same indication. The therapeutical activity is obtained quickly after oral or parenteral administration and is maintained for a relatively long time.

However, the agents of the above-mentioned type, particularly the compounds known as thalidomides, have a serious disadvantage residing in the embryotoxic (teratogenous) secondary effects, which occur after the administration to pregnant women and often result in serious malformations of the infant. In spite of their undeniable advantages outlined above, the use of these agents has been entirely prohibited in numerous countries for the reasons given.

The present invention is based on the discovery that this undesired embryotoxic activity is due to a specific part of the structure, namely, the aromatic phthalimide structure.

Surprisingly it has been found that the use of other dicarboxylic acids having cyclic, bicyclic and related ring systems rather than of phthalic acid results in previously unknown compounds, which are of therapeutic significance and have qualitatively the same pharmacological activities as the previously known succinimides and glutarimides of the class defined initially hereinbefore, whereas the danger of an occurrence of teratogenous effects is entirely eliminated with these new compounds.

The compounds according to the invention have the general formula



wherein

A represents a saturated or unsaturated, substituted or unsubstituted, bivalent hydrocarbon radical,

B represents a saturated or unsaturated, substituted or unsubstituted, bivalent hydrocarbon radical, an oxygen atom or two hydrogen atoms, each of

X_1 and X_4 represents hydrogen, halogen or a substituted or unsubstituted alkyl group, each of

X_2 and X_3 represents hydrogen, halogen, a substituted or unsubstituted alkyl group or part of a double bond formed by said X_2 and X_3,

Y represents a nitrogen atom having its third valency saturated by hydrogen or hydrocarbon radical, and each n represents 0, 1 or

2 which may be the same or different value from that represented by the other n. The bivalent hydrocarbon radicals represented by A and/or B may have a linear, branched chain, cyclic, bicyclic, aromatic or polynuclear configuration, the simplest radicals being the methylene, ethylene and vinylidene radicals. The substituents which may be present in the substituted hydrocarbon radicals A and/or B include halogen, alkyl, aryl, cycloalkyl, aralkyl, alkylidene and arylidene groups. The substituents in the substituted alkyl groups X_1—X_4 are preferably oxygen or oxygen containing groups.

A preferably represents the groups $-CH_2-CH_2-$, $-CH=CH-$ and *o*-phenylene, B preferably represents two hydrogen atoms, a methylene or ethylene radical or an oxygen atom. Further examples of B are phenylene, isopropylene, diphenylethylene or substituted methylene radicals, such as $CH_3-HC<$ and $Cl_2C<$.

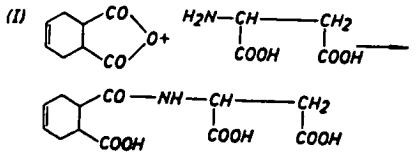
Examples of substituents on the imide nitrogen are methyl, ethyl, any of the various propyl, butyl, allyl groups; cyclohexyl, aryl, aralkyl and alkaryl groups, e.g. phenyl, benzyl, *p*-toluyl.

These novel compounds can be produced from the product obtained when the corresponding cyclic or polycyclic dicarboxylic acids, which can easily be obtained as products of Diels-Alder reactions, or reactive functional derivatives thereof, particularly their anhydrides, chlorides or esters, are reacted with aminodicarboxylic acids, e.g. with alpha-amino-succinic acid (aspartic acid) or alpha-aminoglutaric acid (glutamic acid), or reactive functional derivatives thereof, such as their esters, amides, diamides or imides. This product is then cyclised by reaction with a dehydrating agent and, if necessary, then converted to the desired imide of the invention.

Either or both of the first and second stages of the above process may be carried out in the range of 20°C to 50°C and may be carried out under superatmospheric pressure. If desired a solvent may be employed, preferably one which is capable of promoting the reaction. Such solvents may be an organic base, e.g. pyridine, quinoline or dimethylformamide. The first stage also may be carried out in the presence of a condensation agent especially one which is capable of combining with the eliminated molecule. The second stage, of course, is carried out in the presence of a dehydrating agent.

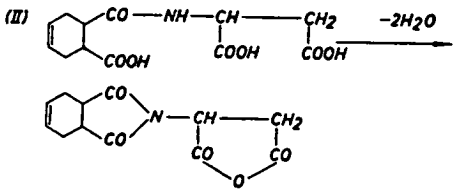
To facilitate further understanding, this reaction will be explained with reference to tetrahydrophthalic anhydride as an example of the (poly)cyclic dicarboxylic acid and to aspartic acid as an example of the aminocarboxylic component. The following reaction results in the first stage of this process: —

(I)



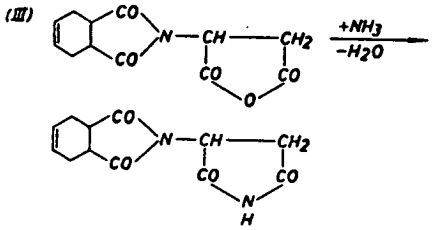
The intermediate product obtained in reaction (I) is cyclised by treatment with a dehydrating agent, such as acetic anhydride, acetyl chloride or $POCl_3$, into the corresponding dicarboximidosuccinic anhydrides, thus: —

(II)



Finally, the anhydride is reacted with ammonia, its salts, such as NH_4Cl or $(NH_4)_2CO_3$ or other NH_3-delivering compounds, such as urea, thiourea, guanidine, guanidine salts, formamide, or acetamide to form the cyclic imide; thus: —

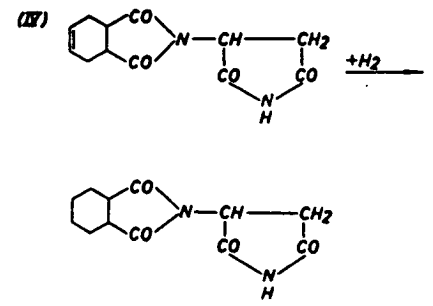
(III)



Instead of ammonia, primary amines or compounds which can liberate primary amines *in situ* may be used in the immediately preceding reaction step so that the corresponding N-substituted succinic imides are obtained.

If the resulting products contain double bonds capable of hydrogenation, they may be transformed in the usual manner into the saturated compounds. If two or more double bonds capable of hydrogenation and of different reactivity are present, one of them or part of them may be selectively saturated (partial hydrogenation).

(IV)



This catalyst hydrogenation may be carried out under superatmospheric pressure.

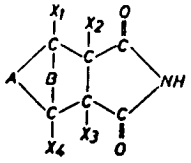
The process which has been outlined hereinbefore may be modified in various ways. A listing of all modifications which are possible is impossible for reasons of space. The Examples which will be given hereinafter are intended only to illustrate the multiplicity of the existing possibilities. The fact that any specific synthesis route is not mentioned has no restricting significance.

As has been mentioned above, the cyclic imides of aminodicarboxylic acids rather than the free aminodicarboxylic acids may be used in the first reaction step so that the starting products are subjected to the transformation of the anhydride into an imide otherwise carried out in step III.

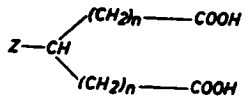
Monoamides of aminodicarboxylic acids, e.g., asparagine, glutamine, isoasparagine or isoglutamine, may be used instead of the free aminodicarboxylic acids to obtain the end product of step III in the second reaction step.

The same applies to the use of the diamides. In this case the cyclization (according to step III) takes place with elimination of NH_3.

The introduction of the other imide group into the compounds according to the invention may be similarly modified. For instance, the imides of the invention may be prepared by a process comprising the steps of (a) reacting a first reactant consisting of a reactive derivative of a carboximide having the general structure



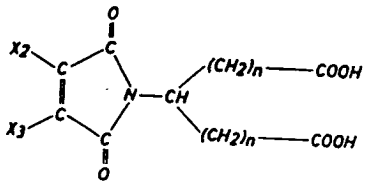
wherein A, B, X_1—X_4 have the same meaning as in claim 1, with a second reactant consisting of a halodicarboxylic acid having the general formula



wherein Z represents Cl, Br or I, or a reactive functional derivative of such halodicarboxylic acid; (b) cyclising the product of step (a) by reaction with a dehydrating agent; and, if necessary, (c) converting the product of (b) to the desired imide product.

Either or both of the first and second stages of the above process may be carried out in the range 20°C to 250°C and may be carried out under superatmospheric pressure. If desired a solvent may be employed, preferably one which is capable of promoting the reaction. Such solvents may be an organic base, e.g. pyridine, quinoline or dimethylformamide. The first stage also may be carried out in the presence of a condensation agent especially one which is capable of combining with the eliminated molecule. The second stage, of course, is carried out in the presence of a dehydrating agent, e.g., the reaction of the potassium salt of 1,4 - endomethylene - Δ^5 - cyclohexane - 2,3 - dicarboxylic imide with diethyl alpha-bromosuccinate results in the formation of diethyl 1,4 - endomethylene - Δ^5 - cyclohexane - 2,3 - dicarboximidosuccinate. This ester is transformed into the imide (according to (III) by a reaction with NH_3, followed by treatment with acetyl chloride.

In other modification of the process, the Diels-Alder reaction to form the cyclic or polycyclic dicarboxylic component is carried out at the end of the sequence of reactions. Thus, imides of the invention may be prepared by a process comprising the step of (a) subjecting a first reactant consisting of a maleinimidodicarboxylic acid having the general formula



or a reactive functional derivative thereof wherein X_2 and X_3 have the same meanings as in claim 1, or a derivative thereof, to a Diels-Alder reaction with a conjugated diene and if necessary (b) converting the product so obtained to the imide product. For instance, alphamaleinimidoglutarimide reacts with conjugated dienes to form the corresponding cyclic or polycyclic dicarboximidoglutarimides.

The compounds according to the invention may be used as therapeutics alone or in combination with other agents and adjuvants or as intermediates in the preparation of therapeutics. They may also be used as starting products of further syntheses.

EXAMPLE 1

20 grams DL-aspartic acid and 23 grams Δ^4 - cyclohexane - 1,2, - cis - dicarboxylic anhydride were boiled in 80 ml absolute pyridine to complete dissolution. The solvent was then removed in vacuo and the residue together with 50 ml acetic anhydride was shortly heated to the boil. Δ^4 - cyclohexene - 1,2 - cis - dicarboximidosuccinic anhydride crystallized upon cooling. Melting point 192—193°C. Yield 31.5 grams. $C_{12}H_{11}NO_5$ (249.22): Calculated 5.62% N, found 5.6% N.

25 grams of the above anhydride were finely ground together with 10 grams urea and the resulting mixed powders were heated on an oil bath to 180°C. for 30 minutes. The cooled mass was dissolved in dimethylformamide (DMF). Δ^4 - cyclohexen - 1,2 - cis - dicarboximidosuccinimide precipitated upon addition of water. Melting point 190—192°C., yield 19.5 grams.

$C_{12}H_{12}N_2O_4$ (248.24): Calculated 11.29% N, found 11.17% N.

The same product was obtained in analogous experiments in which ammonium chloride, ammonium carbonate, thiourea, guanidine sulfate or acetamide was used rather than urea.

Hydrogenation: The above imide was dissolved in ethanol and hydrogenated in the presence of charcoal-supported palladium catalyst. The catalyst was filtered off and the solvent was removed in vacuo. The resulting cyclohexane - 1,2 - cis - dicarboximidosuccinimide has a melting point of 156—158°C.

$C_{12}H_{14}N_2O_4$ (250.25): Calculated 11.20% N, found 11.15% N.

EXAMPLE 2

20 grams DL-aspartic acid and 25 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride were reacted in the procedure of Example 1 to form the 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido - succinic anhydride, melting point 170—171°C., yield 36.5% grams.

30 grams of the above anhydride together with 20 grams ammonium carbonate were heated to 180—200°C. for 30 minutes. The mass was cooled and dissolved in water. The solution was completely extracted with ether in an extractor. The ether solution was evaporated and the residue was dissolved in aqueous acetone, from which 1,4 - endomethylene - Δ^5 - cyclohexen - 2,3 - endo - cis - dicarboximidosuccinimide was crystallized. Melting point 212—213°C., yield 21 grams.

$C_{13}H_{12}N_2O_4$ (260.25): Calculated 10.77% N, found 10.90% N.

Hydrogenation of the above imide in the procedure of Example 1 resulted in 1,4 - endomethylene - cyclohexane - 2,3 - endo-cis - dicarboximidosuccinimide, melting point 260—262°C.

$C_{13}H_{14}N_2O_4$ (262.26): Calculated 10.68% N, found 10.86% N.

EXAMPLE 3

38 grams L-glutamic acid and 40 grams Δ^4 - cyclohexene - 1,2 - cis - dicarboxylic anhydride were boiled in 120 ml pyridine to complete dissolution. The pyridine was then distilled off and the residue was heated together with 120 ml acetic anhydride. The volatile matter was then removed in vacuo. Grinding the residue in ether resulted in the formation of crystalline Δ^4 - cyclohexen - 1,2 - cis - dicarboximidoglutaric anyhdride, melting point 166—167°C.

$C_{13}H_{14}NO_5$ (263.24): Calculated 5.32% N, found 5.27% N.

12 grams of the above anhydride were reacted in the procedure of Example 1 with 6 grams urea to form Δ^4 - cyclohexene - 1,2 - cis - dicarboximidoglutarimide. Melting point 194—195°C.

$C_{13}H_{14}N_2O_4$ (262.26): Calculated 10.68% N, found 10.59% N.

The hydrogenation of the above imide in the procedure of Example 1 resulted in cyclohexane - 1,2 - cis - dicarboximidoglutarimide. Melting point 180—181°C.

$C_{13}H_{16}N_2O_4$ (264.28): Calculated 10.60% N, found 10.66% N.

EXAMPLE 4

29 grams L-glutamic acid and 30 grams cyclohexane - 1,2 - cis - dicarboxylic anhydride were reacted in the procedure of Example 1 to form cyclohexane - 1,2 - cis - dicarboximidoglutaric anhydride, melting point 171—172°C.

$C_{13}H_{13}NO_5$ (285.27): Calculated 5.28% N, found 5.26% N.

The above anhydride was transformed in the procedure of Example 1 into cyclohexane-1,2 - cis - dicarboximidoglutarimide, melting point 180—181°C. This product proved to be identical to that described in Example 3.

$C_{13}H_{16}N_2O_4$ (262.28): Calculated 10.60% N, found 10.51% N.

EXAMPLE 5

29 grams L-glutamic acid and 30 grams cyclohexane - 1,2 - trans - dicarboxylic anhydride were reacted in the procedure of Example 1 to form cyclohexane -1,2 - cis - dicarboximidoglutaric anhydride, melting point 170—172°. By its mixed melting point and its infrared spectrum, this product was proved to be identical to the intermediate anhydride described in Example 4.

EXAMPLE 6

45 grams L-glutamic acid and 53 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride were boiled together with 150 ml pyridine for two hours. After cooling, the mixture was filtered and evaporated in vacuo. The residue was boiled up with 100 ml acetic anhydride and re-evaporated to one half its volume. Part of the resulting 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride crystallized upon cooling and was filtered off. An addition of ether to the mother liquor resulted in a quantitative precipitation. Melting point 175—176°C.

$C_{14}H_{13}NO_5$ (275.28): Calculated 5.09% N, found 5.14% N.

27 grams of the above anhydride were reacted together with 12 grams urea in the procedure of Example 1. The first precipitate consisted of 18 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutarimide. Further amounts of this product were recovered by an exhaustive extraction of the aqueous solution with ether in the procedure of Example 2.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22% N, found 10.29% N.

The hydrogenation of the above imide in the procedure of Example 1 resulted in 1,4-endomethylene - cyclohexane - 2,3 - endo - cis - dicarboximidoglutarimide, melting point 235—236°C.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14% N, found 10.21% N.

Example 7

32.5 grams L-glutamic acid and 36 grams 1,4 - endo - methylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboxylic anhydride were reacted in the procedure of Example 6 to form 1,4 - endo - methylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboximidoglutaric anhydride, melting point 214—216°C.

$C_{14}H_{13}NO_5$ (275.25): Calculated 5.09% N, found 5.06% N.

In the procedure of Example 1, the above anhydride was transformed into 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboximidoglutarimide, melting point 241—243°C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22% N, found 10.19% N.

The hydrogenation of the above imide in the procedure of Example 1 resulted in 1,4-endomethylenecyclo - hexane - 2,3 - exo - cis - dicarboximidoglutarimide, melting point 259—260°C.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14% N, found 10.05% N.

Example 8

45 grams L-glutamic acid and 53 grams 1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboxylic anhydride were reacted in the procedure of Example 6 to form 1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximidoglutaric anhydride, melting point 215—216°C.

$C_{14}H_{15}NO_5$ (277.28): Calculated 5.05% N, found 5.12% N.

5 grams of the above anhydride were charged into 30 ml concentrated ammonia. The solution was allowed to stand for several hours and then evaporated. The residue was boiled for one hour together with 30 ml acetic anhydride, then completely dried in vacuo. The glassy residue was dissolved in aqueous dimethylformamide, from which 1,4-endomethylene - cyclohexane - 2,3 - endo - cis - dicarboximidoglutarimide was crystallized. Melting point 235°C. The mixed melting point and the infrared spectrum proved this product to be identical to that obtained in Example 6.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14% N, found 10.29% N.

Example 9

41.5 grams L-glutamic acid and 50 grams 1,4 - endoethylene - Δ^5 - cyclohexen - 2,3 - endo - cis - dicarboxylic anhydride were reacted in the procedure of Example 6 to form 1,4 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride, melting point 246—248° C.

$C_{15}H_{15}NO_5$ (289.28): Calculated 4.84% N, found 4.84% N.

In the procedure of Example 1, the above anhydride was transformed into 1,5 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutarimide, melting point 240—242°C.

$C_{15}H_{16}N_2O_4$ (288.29): Calculated 97.2% N, found 9.74% N.

The hydrogenation of the above imide in the procedure of Example 1 resulted in 1,4-endoethylenecyclohexane - 2,3 - cis - dicarboximidoglutarimide, melting point 248—250° C.

$C_{15}H_{18}N_2O_4$ (290.31): Calculated 9.65% N, found 9.72% N.

Example 10

29.4 grams L-glutamic acid and 35.6 grams methyl - 1,4 - endomethylene - Δ^5 - cyclohexane - 2,3 - cis - dicarboxylic anhydride (Diels-Alder adduct of maleic anhydride and methyl cyclopentadiene) were reacted in the procedure of Example 1. The product corresponding to methyl - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - cis - dicarboximidoglutaric anhydride was crystallized only with difficulty and was subjected to further processing without purification. Part of the product was crystallized out of a mixture of glacial acetic acid and acetic anhydride for analysis. Melting point 171—173°C.

$C_{15}H_{15}NO_5$ (289.28): Calculated 4.84% N, found 4.98% N.

The above product was transformed into methyl - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - cis - dicarboximidoglutarimide by heating with ammonium carbonate in the procedure of Example 2. Melting point 204—208°C.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72% N, found 9.78% N.

Example 11

18.3 grams L-glutamic acid and 21 grams 1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboxylic acid were boiled in 100 ml pyridine to complete dissolution. The pyridine was then largely removed in vacuo. The residue was dissolved in dilute H_2SO_4 and the

solution was exhaustively extracted with ether. The residue obtained by the distillation of the ether was boiled up together with 40 ml acetic anhydride. 1,4 - endoxo - cyclohexane - 2,3 - exo - cis - dicarboximidoglutaric anhydride crystallized upon cooling. Melting point 219—220°C., yield 19.7 grams.

$C_{13}H_{13}NO_6$ (279.24): Calculated 5.02% N, found 4.96% N.

16 grams of the above anhydride were reacted with 10 grams urea in the procedure of Example 1 to form 1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboximidoglutarimide, melting point 329—330°C., yield 13 grams.

$C_{13}H_{14}N_2O_5$ (278.26): Calculated 10.07% N, found 10.19% N.

Example 12

16.3 grams L-glutamic acid and 41.2 grams 1,4,5,6,7,7 - hexachloro - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride (Diels-Alder adduct of maleic anhydride and hexachlorocyclopentadiene) were reacted in the procedure of Example 1 to form 1,4,5,5,6,7,7-hexachloro - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride, melting point 235—240°C., yield about 25 grams.

$C_{14}H_7Cl_6NO_5$ (481.97): Calculated 2.91% N, found 3.01% N.

18 grams of the above anhydride were reacted with 10 grams urea in the procedure of Example 1 to form 1,4,5,6,7,7 - hexachloro - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutarimide, melting point 266—268°C., yield 14 grams.

$C_{14}H_8Cl_6N_2O_4$ (480.98): Calculated 5.82% N, 44.24% Cl, found 5.67% N, 43.75% Cl.

Example 13

29.5 grams L-glutamic acid and 55.5 grams 5,6; 7,8 - dibenzo - bicyclo(2,2,2)octane - 2,3 - cis - dicarboxylic anhydride (Diels-Alder adduct of maleic anhydride and anthracene) were reacted in the procedure of Example 1 to form 5,6; 7,8 - dibenzo - bicyclo-(2,2,2)octane - 2,3 - cis - dicarboximidoglutaric anhydride. Melting point 283—285°C. Yield 58 grams.

$C_{23}H_{17}NO_5$ (387.39): Calculated 3.62% N, found 3.69% N.

The above anhydride was transformed into 5,6; 7,8 - dibenzo - bicyclo(2,2,2)octane - 2,3 - dicarboximidoglutarimide by heating with urea or ammonium carbonate. Melting point 283—284°C.

$C_{23}H_{18}H_2O_4$ (386.41): Calculated 7.25% N, found 7.27% N.

Example 14

6.7 grams L-glutamic acid and 15 grams 7 - diphenyl - methylene - 1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboxylic anhydride (partially hydrogenated Diels-Alder adduct of maleic anhydride and diphenylfulvene) were reacted in the procedure of Example 1 to form 7 - diphenylmethylene - 1,4 - endomethylene - cyclohexane - 2,3 - endo - cis - dicarboximidoglutaric anhydride, melting point 254—256°C.

$C_{27}H_{23}NO_5$ (441.49): Calculated 3.17% N, found 3.22% N.

The above anhydride was transformed in the procedure of Example 1 into 7 - diphenylmethylene - 1,4 - endomethylene - cyclohexane - 2,4 - endo - cis - dicarboximidoglutarimide, melting point 210—212°C.

$C_{27}H_{24}N_2O_4$ (440.51): Calculated 6.36% N, found 6.23% N.

Example 15

20 grams of a freshly prepared potassium compound of 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic acid imide and 25 grams diethyl alpha-bromosuccinate were heated together with 100 ml dimethylformamide on the water bath for one hour. After cooling, the solvent was removed in vacuo. The residue was received in water and repeatedly shaken with ether. The combined ether extracts were dried over Na_2SO_4, filtered and evaporated. The resulting diethyl-alpha - (1,4 - endo - methylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - succinate was dissolved in absolute ethanol without further purification. The solution was saturated with dry ammonia gas with stirring and cooling and was then left undisturbed for a prolonged time. It was thereafter evaporated to dryness in vacuo. The residue was treated with 50 ml acetyl chloride, re-evaporated and finally received in glacial acetic acid. Storage in a refrigerator caused part of the resulting 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidosuccinimide to crystallize. Further parts precipitated upon dilution with water. Melting point 212—213°C.

$C_{13}H_{12}N_2O_4$ (260.25): Calculated 10.77% N, found 10.82% N.

Example 16

10 grams L-alpha-aminosuccinic acid-gamma-amide (L-asparagine) and 12.5 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride were boiled in 50 ml pyridine to complete dissolution. The pyridine was then largely removed in vacuo. 430 ml acetyl chloride were added to the residue. The resulting mixture was heated on the water bath for one hour and was then evaporated. When the cooled mass was ground with acetone, 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidosuccinimide was crystallized. Melting point 212°C., yield 11.5 grams.

$C_{13}H_{12}N_2O_4$ (260.25): Calculated 10.77% N, found 10.68% N.

EXAMPLE 17

10 grams L-alpha-aminoglutaric acid-delta-amide (L-glutamine) and 11.5 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride were reacted in the procedure of Example 16 to form 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutarimide, melting point 235—236°C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22% N, found 10.09% N.

EXAMPLE 18

10 grams DL-alpha-aminoglutarimide and 15 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride were boiled in 50 ml pyridine. The solution was filtered and evaporated in vacuo. The residue was shortly boiled with a little glacial acetic acid and acetic anhydride. 1,4-endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutarimide crystallized together with other products upon storage in a refrigerator and was obtained in a pure state by reueated recrystallization from aqueous dimethylformamide. Melting point 235°C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22% N, found 9.98% N.

EXAMPLE 19

27.5 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride obtained by the procedure of Example 6 were finely ground with 77.5 grams methylamine hydrochloride and heated to 180—190°C. on an oil bath for one hour. The cooled mass was received in acetone. The surplus methylamine hydrochloride separated and was removed. The product was freed from acetone and recrystallized from aqueous dimethylformamide: N - methyl - alpha - (1,4 - endo - methylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 153—154°C., yield about 24 grams.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72% N, found 9.88% N.

EXAMPLE 20

5.5 grams N - methyl - alpha - (maleinimido) - glutarimide were dissolved in 40 milliliters dimethylformamide and 5 grams freshly distilled cyclopentadiene were added to the solution. When the latter had been stored for 24 hours, it was evaporated in vacuo to one third of its original volume. After an addition of water and storage in a refrigerator, N - methyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexen - 2,3 - endo - cis - dicarboximido) - glutarimide was crystallized. Melting point 152—154°C.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72% N, found 9.84% N.

EXAMPLE 21

27.5 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride obtained by the procedure of Example 6 were melted together with 10 grams benzylamine. The cooled mass was dissolved in aqueous dimethylformamide whereby N - benzyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide was crystallized. Melting point 137—138°C.

$C_{21}H_{20}N_2O_4$ (364.39): Calculated 7.71% N, found 7.75% N.

The above imide was hydrogenated to produce N - benzyl - alpha - (1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 168—170°C.

$C_{21}H_{22}N_2O_4$ (366.41): Calculated 7.65% N, found 8.03% N.

Analogous procedures resulted in the formation of: N - phenyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 220°C.; N - phenyl - alpha - (1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 212°C.; N - *p* - toluyl) - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 243°C.; N - (*p* - toluyl) - alpha - (1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 232°C.; N - cyclohexyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, glassy mass.

EXAMPLE 22

1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride produced by the procedure of Example 6 was charged in small increments with stirring into an aqueous solution of a surplus of methylamine and was allowed to stand overnight at room temperature. The solution was then evaporated in vacuo to dryness. The glassy residue was boiled up together with an equal amount of acetic anhydride and re-evaporated in vacuo. The residue was dissolved in ethanol. N - methyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide was crystallized from the solution. Melting point 153—154°C. This product was identical to that obtained in Example 19.

Hydrogenation: The above product was hydrogenated in the presence of a charcoal-supported palladium catalyst. This was followed by filtering and evaporation in vacuo. The residue was dissolved in ethanol, from which N - methyl - alpha - (1,4 - endo-

methylenecyclohexane - 2,3 - endo - cis - dicarboximido) - glutarimide was crystallized. Melting point 138—139°C.

$C_{15}H_{18}N_2O_4$ (290.32): Calculated 62.05% C, 6.25% H, 9.65% N; found 62.04% C, 6.21% H, 9.70% N.

Analogous procedures resulted in the formation of: N - ethyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 147—148° C.; N - propyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, oily; N - n - butyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo-cis - dicarboximido) - glutarimide, melting point 186°C.; N - allyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3, endo - cis - dicarboximido) - glutarimide, oily; N - t - butyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 198°C.

Example 23

20 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboximidoglutaric anhydride produced in the procedure of Example 7 were heated together with 10 grams methylamine hydrochloride at 180—190°C. for one hour. The cooled mass was dissolved in a little dimethylformamide, diluted with water and extracted with ether. The ether extract was evaporated, The residue was dissolved in ethanol, from which N - methyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboximido)-glutarimide was crystallized. Melting point 170—172°C.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72% N, found 9.84% N.

The hydrogenation of the above product resulted in N - methyl - alpha - (1,4 - endomethylenecyclohexane - 2,3 - exo - cis - dicarboximido) - glutarimide, melting point 181°C.

$C_{15}H_{18}N_2O_4$ (290.32): Calculated 62.05% C, 6.25% H, 9.65% N; found 61.89% C, 6.20% H, 9.70% N.

Example 24

14.5 grams 1,4 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride obtained by the procedure of Example 9 were reacted with methylamine hydrochloride in the procedure of Example 25. N - methyl - alpha - (1,4 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - glutarimide, melting point 185—186°C.

$C_{16}H_{18}N_2O_4$ (303.54): Calculated 9.27% N, found 9.18% N.

The above product was hydrogenated to form N - methyl - alpha - (1,4 - endoethylenecyclohexane - cis - dicarboximido) - glutarimide, melting point 160—161°C.

Example 25

The 1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboximidoglutaric anhydride obtained by the procedure of Example 11 was reacted with methylamine hydrochloride in the procedure of Example 23. N - methyl - alpha - (1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboximido) - glutarimide, melting point 290—293°C.

Example 26

40 grams DL-aspartic acid and 55 grams 1,4 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride were reacted in the procedure of Example 1. Yield: 67 grams 1,4 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidosuccinic anhydride, melting point 212—213°C.

$C_{14}H_{13}NO_5$ (275.25): Calculated 5.09% N, found 4.97% N.

The above product was reacted in the procedure of Example 1 with urea to form 1,4-endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidosuccinimide, melting point 207—208°C.

The last-mentioned compound was hydrogenated to form 1,4 - endoethylenecyclohexane - 2,3 - cis - dicarboximidosuccinimide, melting point 234—235°C.

Example 27

26.6 grams DL-aspartic acid and 33 grams 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboxylic anhydride were reacted in the procedure of Example 2 to form 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboximidosuccinic anhydride, melting point 195—196°C.

$C_{13}H_{11}NO_5$ (261.23): Calculated 5.36% N, found 5.37% N.

The above product was transformed by the procedure of Example 2 into 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - exo - cis - dicarboximidosuccinimide, melting point 180—182°C.

The above compound was hydrogenated to form 1,4 - endomethylenecyclohexane - 2,3 - exo - cis - dicarboximidosuccinimide, melting point 200—202°C.

Example 28

25 grams DL-aspartic acid and 31.5 grams 1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboxylic anhydride were reacted in the procedure of Example 1 to form 1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboximidosuccinic anhydride. Yield 42 grams, melting point 216—218°C.

$C_{12}H_{11}NO_6$ (265.22): Calculated 5.28% N, found 5.12% N.

The above product was reacted with urea to form 1,4 - endoxocyclohexane - 2,3 - exo -

cis - dicarboximidosuccinimide, melting point 225—226°C.

EXAMPLE 29

10 g 1,4 - endoxomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidosuccinic anhydride prepared by the procedure of Example 2 were kept together with 5 grams methylamine hydrochloride in a molten state at 170—180°C. for one hour. The cooled mass was washed with water and dissolved in aqueous alcohol, from which N - methyl - alpha - (1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - succinimide was crystallized. Melting point 135—136°C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22% N, found 10.32% N.

The above product was hydrogenated to form N - methyl - alpha - (1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximido) - succinimide, melting point 138—139°C.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14% N, found 10.15% N.

EXAMPLE 30

1,4 - endoethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidosuccinic anhydride prepared by the procedure of Example 26 was transformed into N - methyl - alpha - (1,4 - endo - ethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximido) - succinimide in a procedure which is analogous to that of Example 29. Melting point 188—190°C.

$C_{15}H_{16}N_2O_4$ (288.29): Calculated 9.27% N, found 9.75% N.

The above product was hydrogenated to form N - methyl - alpha - (1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximido) - succinimide, melting point 155°C.

$C_{15}H_{18}N_2O_4$ (290.31): Calculated 9.65% N, found 9.59% N.

EXAMPLE 31

1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboximidosuccinic anhydride prepared by the procedure of Example 28 was transformed into N - methyl - alpha - (1,4 - endoxocyclohexane - 2,3 - exo - cis - dicarboximido) - succinimide in a procedure which is analogous to that of Example 29. Melting point 320°C.

$C_{13}H_{14}N_2O_5$ (278.26): Calculated 10.07% N, found 9.96% N.

EXAMPLE 32

30 grams L-glutamic acid and 36 grams 2 - exomethyl - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboxylic anhydride (adduct of citraconic anhydride and cyclopentadiene) were reacted and processed in the procedure of Example 1 to form 2-exomethyl - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutaric anhydride, melting point 204—205°C.

$C_{15}H_{15}NO_5$ (289.28): Calculated 4.84% N, found 4.15% N.

The above product was transformed by the procedure of Example 1 into 2 - exomethyl - 1,4 - endomethylene - Δ^5 - cyclohexene - 2,3 - endo - cis - dicarboximidoglutarimide, melting point 210°C.

Hydrogenation resulted in 2 - exomethyl - 1,4 - endo - methylenecyclohexane - 2,3 - endo - cis - dicarboximidoglutarimide, melting point 173°C.

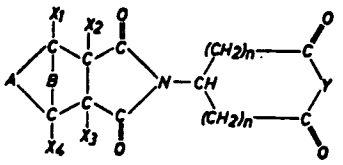
$C_{15}H_{18}N_2O_4$ (290.31): Calculated 9.65% N, found 9.55% N.

In an analogous procedure, 2 - exomethyl - 1,4 - endo - methylenecyclohexane - 2,3 - endo - cis - dicarboxylic anhydride was transformed into an intermediate anhydride, 2-exomethyl - 1,4 - endomethylenecyclohexane - 2,3 - endo - cis - dicarboximidoglutaric anhydride, melting point 165°C.

$C_{15}H_{17}NO_5$ (291.30): Calculated 4.80% N, found 5.12% N. This anhydride can be converted as above into the corresponding imides.

WHAT I CLAIM IS:—

1. A compound having the general formula



I

wherein

A represents a saturated or unsaturated, substituted or unsubstituted, bivalent hydrocarbon radical,

B represents a saturated or unsaturated, substituted or unsubstituted, bivalent hydrocarbon radical, an oxygen atom or two hydrogen atoms, each of

X_1 and X_4 represents hydrogen, halogen or a substituted or unsubstituted alkyl group, each of

X_2 and X_3 represents hydrogen, halogen, a substituted or unsubstituted alkyl group or part of a double bond formed by said X_2 and X_3,

Y represents a nitrogen atom having its third valency saturated by hydrogen or a hydrocarbon radical, and

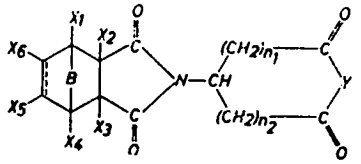
each n represents 0, 1 or 2, which may be the same or different value from that of the other n.

2. A compound as claimed in claim 1, in which at least one of said hydrocarbon radicals represented by A and B is a methylene, ethylene or vinylidene group or a larger radical of linear, branched chain, cyclic, bicyclic, aromatic, and polynuclear configuration.

3. A compound as claimed in claim 1 or 2,

in which at least one of said hydrocarbon radicals represented by A and B has a substituent consisting of a halogen, alkyl, aryl, cycloalkyl, aralkyl, alkylidene or arylidene group.

4. A compound having the general formula



wherein

B represents two hydrogen atoms, $-CH_2-$, $-CH_2-CH_2-$ or $-O-$; Y represents $>NR$, wherein R represents hydrogen or a hydrocarbon radical, each of

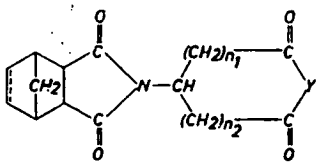
X_1 to X_6 represents hydrogen, halogen or alkyl,

n_1 represents zero or 1, and

n_2 represents 2, provided that n_1 is zero, or 1.

5. A compound as claimed in claim 4, which comprises a double bond in the Δ^5 position.

6. A compound having the general formula



wherein

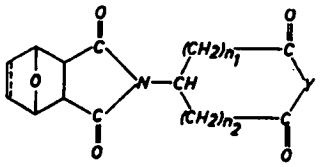
Y represents $>NR$, wherein R represents hydrogen or an alkyl group,

n_1 represents zero or 1, and

n_2 represents 2, provided that n_1 is zero, or 1.

7. A compound as claimed in claim 6, which comprises a double bond in the Δ^5 position.

8. A compound having the general formula



wherein

Y represents $>NR$, wherein R represents hydrogen or an alkyl group,

n_1 represents zero or 1, and

n_2 represents 2, provided that n_1 is zero, or 1.

9. A compound as claimed in claim 8, which comprises a double bond in the Δ^5 position.

10. A stereo isomer of Δ^4 - Cyclohexene - 1,2 - dicarboximidosuccinimide.

11. A stereo isomer of Cyclohexane - 1,2 - dicarboximidosuccinimide.

12. A stereo isomer of Δ^4 - Cyclohexene - 1,2 - dicarboximidoglutarimide.

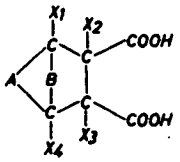
13. A stereo isomer of 1,4 - Endomethylene - Δ^5 - cyclohexene - 2,3 - dicarboximidosuccinimide.

14. A stereo isomer of 1,4 - Endomethylene - Δ^5 - cyclohexene - 2,3 - dicarboximidoglutarimide.

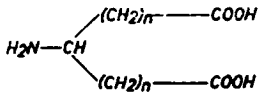
15. A stereor isomer of 1,4 - Endoxocyclohexane - 2,3 - dicarboximidoglutarimide.

16. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 15 and a pharmaceutically acceptible carrier.

17. A process of producing a compound as claimed in any of claims 1 to 3, which process comprises the steps of (a) reacting a first reactant consisting of a dicarboxylic acid having the general structure



wherein A, B, X_1—X_4 have the same meanings as in claims 1, or a reactive functional derivative of such acid, with a second reactant consisting of an aminodicarboxylic acid having the general structure



wherein n is as defined in claim 1, or a reactive functional derivative of such aminodicarboxylic acid; (b) cyclising the product of step (a) by reaction with a dehydrating agent; and, if necessary, (c) converting the product of (b) to the desired imide product.

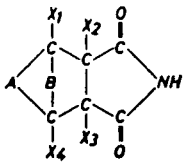
18. A process as claimed in claim 17, in which said first reactant is an anhydride, chloride or ester of such dicarboxylic acid.

19. A process as claimed in claim 17 or 18, in which said second reactant is an ester, amide, diamide or imide of such aminodicarboxylic acid.

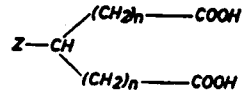
20. A process as claimed in any of claims 17 to 19, in which said aminodicarboxylic acid is aspartic or glutamic acid.

21. A process of producing a compound as claimed in any of claims 1 to 3, which process comprises the steps of (a) reacting a

first reactant consisting of a reactive derivative of a carboximide having the general structure



wherein A, B, X_1—X_4 have the same meanings as in claim 1, with a second reactant consisting of a halodicarboxylic acid having the general formula



wherein Z represents Cl, Br or I, and n is as defined in claim 1, or a reactive functional derivative of such halodicarboxylic acid; (b) cyclising the product of step (a) by reaction with a dehydrating agent; and, if necessary, (c) converting the product of (b) to the desired imide product.

22. A process as claimed in claim 21, in which said first reactant is an alkali compound of such carboximide.

23. A process as claimed in claim 21 or 22, in which said second reactant is an ester or imide of such halodicarboxylic acid.

24. A process as claimed in any one of claims 17 to 23 wherein either or both of the reaction steps (a) and (b) are carried out at a temperature in the range of 20° to 250°C.

25. A process as claimed in any one of claims 17 to 24 wherein either or both of the reaction steps (a) and (b) are carried out under super-atmospheric pressure.

26. A process as claimed in any one of claims 17 to 25 wherein either or both of the reaction steps (a) and (b) are carried out in the presence of a solvent.

27. A process as claimed in claim 26 wherein the solvent is capable of promoting the reaction.

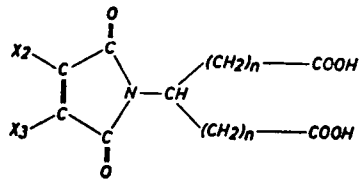
28. A process as claimed in claim 27 wherein the solvent is an organic base.

29. A process as claimed in claim 28 wherein the solvent is pyridine, quinoline or dimethylformamide.

30. A process as claimed in any one of claims 17 to 29 wherein the reaction step (a) is carried out in the presence of a condensation agent.

31. A process as claimed in claim 30 wherein the condensation agent is capable of combining with the eliminated molecule.

32. A process of producing a compound as claimed in any of claims 1 to 3, which process comprises the steps of (a) subjecting a first reactant consisting of a maleinimidocarboxylic acid having the general formula



or a reactive functional derivative thereof wherein X_2 and X_3 and n have the same meanings as in claim 1, to a Diels-Alder reaction with a conjugated diene and if necessary (b) converting the product so obtained to the imide product.

33. A process as claimed in claim 32, in which said first reactant consists of an ester or imide of such maleinimidodicarboxylic acid.

34. A process as claimed in claims 33, in which said first reactant consists of a cyclic derivative of succinic or glutaric acid.

35. A process of producing a compound as claimed in any one of claims 1, 2 or 3 which process comprises subjecting a compound as claimed in any of claims 1 to 3, which has a double bond capable of hydrogenation, to catalytic hydrogenation whereby said compound is transformed into one having a partly or entirely saturated ring system.

36. A process as claimed in claim 35, in which said catalytic hydrogenation is carried out under superatmospheric pressure.

37. A cyclic derivative of succinic or glutaric acid, as claimed in any one of claims 1 to 15, substantially as described hereinbefore.

38. A pharmaceutical composition which comprises a cyclic derivative of succinic or glutaric acid as claimed in claim 37 and a pharmaceutically acceptable carrier.

39. A process as claimed in any one of claims 17 to 36 for producing a cyclic derivative of succinic or glutaric acid, substantially as described hereinbefore.

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